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Synthesis and Antimicrobial activity of Novel 2,6-Diundecylidenecyclohexan-1-One Derivatives

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Abstract

Twelve newly prepared compounds starting from cycloheanone are done. Cyclohexanone reacts with undecanal to afford 2,6-diundecylidenecyclohexan-1-one **1**. 2,6-Diundecylidenecyclohexan-1-one **1** reacts with urea, and thiourea to afford quinazoline derivatives **2a,b**. Cyclohexanone derivative **1** reacts with guanidine, and aminoguanidine to form quinazoline derivatives **3a,b**. Compound **1** reacts with semicarbazide, and thiosemicarbazide to give indazole derivatives **4a,b**. Also, cyclohexanone derivative **1** reacts with carbon disulfide to afford benzo[b]thiophene derivative **5**. Cyclohexanone derivative **1** reacts with hydrazine hydrate, and hydroxylamine to form indazole derivatives **6a,b**. Quinazoline derivative **3b** reacts with p-chlorobenzaldehyde to afford octahydroquinazoline derivative **7**. Also, quinazoline derivative **3b** reacts with ribose, and glucose to afford sugar derivatives **8a,b**. Antimicrobial screening of new prepared compounds was done against G+ve bacteria, G-ve bacteria, and two fungi. Several compounds show promising antimicrobial activity as compared with reference drug used.

Keywords: Diundecylidenecyclohexan-1-one derivatives; quinazoline derivatives; indazole derivatives; benzo[b]oxazole derivatives; benzo[b]thiophene; antimicrobial activity.

1. Introduction

Quinazoline derivatives have different pharmacological activities (1). They have antifungal activity, antimalarial activity, antibacterial activity, antituberculosis activity, anticonvulsant activity, antiviral activity, anti-HIV activity, analgesic activity, poly-(ADP-ribose) polymerase (PARP) inhibitory effect, thymidylate synthase inhibitory effect, and thyrosine kinase inhibitory effect, and anticancer activity (2-9).

There are several drugs on the market that contain quinazoline moiety e.g. doxazosine mesylate, prazosin hydrochloride, and terazosine hydrochloride (Figure 1) (1). Doxazosin mesylate, prazosin hydrochloride, and terazosine hydrochloride are oral antihypertensive drugs used also for treatment of benign prostatic hyperplasia. Alfuzocin is also a commercially available drug that treats benign prostatic hyperplasia which contains quinazoline moiety (Figure 1) (1).

Also, gefitinib and erlotinib are commercially available drugs for treatment of cancer that contain quinazoline derivatives (Figure 1) (1). The mechanism of anticancer activity of quinazoline derivatives is EGFR inhibition, DNA repair enzymes inhibition, inhibition of thymidylate enzyme, and tubulin enzyme inhibition (1).

Also, indazole derivatives have wide range of biological activities e.g. antifungal activity, anticancer activity, antiarryhythmic activity, and anti-HIV activity (10). They are used in the manufacture of polymers, antioxidants, and cosmetics (10). Several commercially available anticancer drugs contain indazole moiety e.g. niraparib, and entrectinib (10). In addition, isoxazole derivatives have a variety of pharmacological activities e.g. antiviral activity, antimicrobial activity, anticancer activity, anti-inflammatory activity, antithrombotic activity, antiplatelet activity, antidiabetic activity, anticonvulsant activity, analgesic activity, and anti-Alzheimer activity (11).

Several isoxazole containing drugs available in the market which used as antibacterial agents e.g. sulfisoxazole, dicloacillin, flucloxacillin, oxacillin, cloxacillin, and sulfamethoxazole (11).

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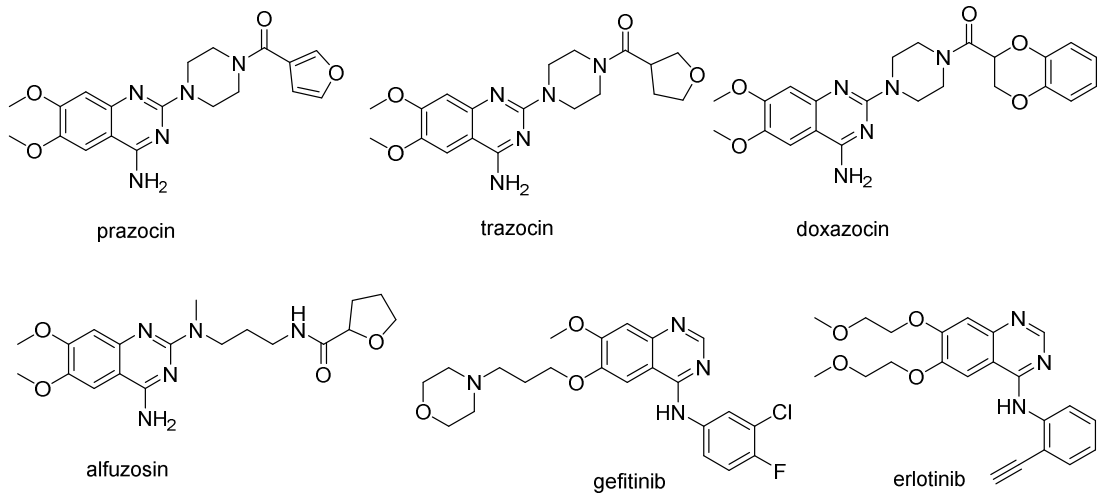


Figure 1: Quinazoline derivatives

All previous biological activities directed us to prepare novel 2,6-diundecylidenecyclohexan-1-one derivatives and antimicrobial screening of the resulted compounds.

2. Experimental

The apparatus used is as previously reported manuscript (12).

2,6-Diundecylidenecyclohexan-1-one **1**

A mixture of cyclohexanone (0.01 mole), and undecanal (0.01 mole) in methanol (50 mL) containing potassium hydroxide (1 gm) is heated on water bath at 50-70 ºC for 30 minutes. The reaction mixture is evaporated under reduced pressure. The residue is extracted with ether. The extract is evaporated to afford compound **1**.Yield: 90%; IR (KBr) cm^{-1}, ν: 1675 (C=O); ^{1}H NMR (DMSO) δ/ppm: 0.75 (t, 6H, j=8 Hz, $2CH_3$), 1.10 (m, 36H, $18CH_2$), 2.00 (m, 2H, CH_2), 2.20 (t, 4H, j=7.1 Hz, $2CH_2$), 5.00 (t, 2H, j=6.2 Hz, 2CH=). ^{13}C NMR (DMSO) δ/ppm: 14.6, 15.1, 17.2, 20.1, 21.2, 22.1, 24.2, 25.3, 26.1, 27.6, 27.8, 29.0, 30.1 ($20CH_2$, $2CH_3$), 148.1, 151.1 (4C=), 161.1 (C=O). MS (m/z): 402.7 (M^+, 61%). Anal. Calcd. for $C_{28}H_{50}O$: C, 83.51; H, 12.52; Found: C, 83.61; H, 12.61.

Preparation of quinazoline derivatives 2a,b

A mixture of cyclohexanone derivative **1** (0.01 mole), and urea or thiourea (0.01mole) is added to methanol (50mL) containing potassium hydroxide (1.5 gm). The reaction mixture is refluxed for one hour. Then, the reaction mixture is evaporated under reduced pressure. The solid formed is extracted with ether. The ether extract is evaporated to give quinazoline derivatives **2a,b**.

4-Decyl-8-undecylidene-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-one **2a**

Yield: 65%; IR (KBr) cm^{-1}, ν: 3410 (NH), 3450 (NH), 1665 (C=O); ^{1}H NMR (DMSO) δ/ppm: 0.80 (t, 6H, j=8 Hz, $2CH_3$), 1.20 (m, 36H, $18CH_2$), 1.28 (m, 2H, CH_2), 1.67 (t, 4H, j=7.1 Hz, $2CH_2$), 3.70 (brs, 2H, 2NH), 4.80 (t, 1H, j=7 Hz, CHN), 5.80 (t, 1H, j=6.2 Hz, CH=). ^{13}C NMR (DMSO) δ/ppm: 14.1, 15.2, 16.4, 17.9, 19.0, 20.9, 22.1, 23.6, 24.5, 24.9, 25.1, 25.3, 27.6, 48.9 (CH, $21CH_2$, $2CH_3$), 118.1, 119.4, 120.0, 121.3 (4CH=), 151.4(C=O). MS (m/z): 444.7 (M^+, 52%). Anal. Calcd. for $C_{29}H_{52}N_2O$: C, 78.32; H, 11.79; N, 6.30; Found: C, 78.41; H, 11.83 N, 6.39.

4-Decyl-8-undecylidene-3,4,5,6,7,8-hexahydroquinazoline-2(1H)-thione **2b**

Yield: 63%; IR (KBr) cm^{-1}, ν: 3410 (NH), 3350 (NH); ^{1}H NMR (DMSO) δ/ppm: 0.10 (t, 6H, j=8 Hz, 2 CH_3), 0.85 (t, 4H, j=7.1 Hz, $2CH_2$), 1.25 (m, 36 H, 18 CH_2), 2.10 (m, 2H, CH_2), 3.80 (t, 1H, j=7 Hz, CH), 4.90 (brs, 2H, 2 NH), 6.60 (t, 1H, j=6.2 Hz, CH=). ^{13}C NMR (DMSO) δ/ppm: 15.6, 16.1, 17.5, 18.2, 19.8, 20.4, 21.3, 22.0, 22.1, 23.1, 23.6, 25.3, 27.6, 43.6 (CH, $21CH_2$, $2CH_3$), 118.2, 119.8, 120.1, 138.0 (4CH=), 162.1 (C=S). MS (m/z): 460.8 (M^+, 58 %). Anal. Calcd. for $C_{29}H_{52}N_2S$: C, 75.59; H, 11.37; N, 6.08; Found: C, 75.67; H, 11.45 N, 6.14.

Preparation of quinazoline derivatives 3a,b

A mixture of cyclohexanone derivative **1** (0.01 mole), and quanidine or aminoguanidine (0.01mole) is added to methanol (50mL) containing potassium hydroxide (1.5 gm). The reaction mixture is refluxed for one hour. Then, the reaction mixture is evaporated under reduced pressure. The solid formed is extracted with ether. The ether extract is evaporated to give quinazoline derivatives **3a,b**.

4-Decyl-8-undecylidene-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-imine **3a**

Yield: 55%; IR (KBr) cm^{-1}, ν: 3420 (NH), 3370 (NH); ^{1}H NMR (DMSO) δ/ppm: 0.70 (t, 6H, j=8 Hz, $2CH_3$), 1.10 (m, 36 H, $18CH_2$), 1.50 (t, 4H, j=7.1, $2CH_2$), 2.20 (m, 2H, CH_2), 3.60 (t, 1H, j=7 Hz, CH), 3.90 (brs, 3H, 3NH), 6.20 (t, 1H, j=6.2 Hz, CH=). ^{13}C NMR (DMSO) δ/ppm: 16.1, 17.4, 17.9, 19.0, 19.4, 20.9, 21.3, 22.0, 22.7, 23.6, 24.5, 25.1, 25.3, 40.6 (CH, $21CH_2$, $2CH_3$), 119.2, 119.9, 120.1, 136.9 (4CH=), 156.4 (C=N). MS (m/z): 443.7 (M^+, 48%). Anal. Calcd. for $C_{29}H_{53}N_3$: C, 78.49; H, 12.04; N, 9.47; Found: C, 78.55; H, 12.15 N, 9.54.

4-Decyl-2-hydrazono-8-undecylidene-1,2,3,4,5,6,7,8-octahydroquinazoline **3b**

Yield: 53%; IR (KBr) cm^{-1}, ν: 3480 (NH), 3450 (NH), 3410 (NH_2); ^{1}H NMR (DMSO) δ/ppm: 0.05 (t, 6H, j=8 Hz, $2CH_3$), 0.75 (t, 4H, j=7.1 Hz, $2CH_2$), 1.15 (m, 36H, $18CH_2$), 1.50 (m, 2H, CH_2), 2.2 (brs, 4H, 2NH, NH_2), 3.60 (t, 1H, j=7 Hz, CHN), 6.90 (t, 1H, j=6.2 Hz, CH=). ^{13}C NMR (DMSO) δ/ppm: 17.1, 17.9, 18.3, 18.9, 19.1, 19.6, 20.6, 21.0, 22.1, 22.7, 23.6, 24.0, 25.3, 48.6 (CH, $21CH_2$, $2CH_3$), 120.1, 122.4, 125.8, 138.9 (4CH=), 155.6 (C=N). MS (m/z): 458.7 (M^+, 45%). Anal. Calcd. for $C_{29}H_{54}N_4$: C, 75.92; H, 11.86; N, 12.21; Found: C, 76.02; H, 11.93 N, 12.30.

Preparation of indazole derivatives 4a,b

A mixture of cyclohexanone derivative **1** (0.01 mole), and semicarbazide or thiosemicarbazide (0.01mole) is added to methanol (50mL) containing potassium hydroxide (1.5 gm). The reaction mixture is refluxed for one hour. Then, the reaction mixture is evaporated under reduced pressure. The solid formed is extracted with ether. The ether extract is evaporated to give indazole derivatives **4a,b**.

3-Decyl-7-undecylidene-1,3,4,5,6,7-hexahydro-2H-indazole-2-carboxamide **4a**

Yield: 56%; IR (KBr) cm^{-1}, ν: 3455 (NH), 3410 (NH_2), 1657 (C=O); ^{1}H NMR (DMSO) δ/ppm: 0.05 (m, 36H, $18CH_2$), 0.90 (t, 6H, j=8 Hz, 2 CH_3), 1.30 (t, 4H, j=7.1 Hz, $2CH_2$), 1.30 (brs, 3H, NH, NH_2), 1.80 (m, 2H, CH_2), 3.60 (t, 1H, j=7 Hz, CH), 7.20 (t, 1H, j=6.2 Hz, CH=). ^{13}C NMR (DMSO) δ/ppm: 17.5, 17.9, 18.1, 18.7, 20.0, 21.2, 22.1, 23.0, 23.6, 24.1, 25.3, 26.3, 27.6, 47.9 (CH, $21CH_2$, $2CH_3$), 118.5, 119.7, 120.1, 138.9 (4C=), 161.1 (C=O). MS (m/z): 459.7 (M^+, 45%). Anal. Calcd. for $C_{29}H_{53}N_3O$: C, 75.76; H, 11.62; N, 9.14; Found: C, 75.84; H, 11.71 N, 9.22.

3-Decyl-7-undecylidene-1,3,4,5,6,7-hexahydro-2H-indazole-2-carbothioamide **4b**

Yield: 60%; IR (KBr) cm^{-1}, ν: 3460 (NH), 3417 (NH_2); ^{1}H NMR (DMSO) δ/ppm: 0.05 (m, 36H, $18CH_2$), 0.90 (t, 6H, j=8 Hz, $2CH_3$), 1.10 (t, 4H, j=6. $2CH_2$), 1.10 (brs, 3H, NH, NH_2), 1.50 (m, 2H, CH_2), 7.20 (t, 1H, j=6.2 Hz, CH=). ^{13}C NMR (DMSO) δ/ppm: 19.2, 19.8, 20.0, 20.9, 21.2, 21.8, 22.1, 22.9, 23.6, 25.1, 25.3, 26.0, 27.6, 43.1 (CH, $21CH_2$, $2CH_3$), 118.2, 119.7, 120.5, 138.9 (4C=), 169.1 (C=S). MS (m/z): 475.8 (M^+, 41%). Anal. Calcd. for $C_{29}H_{53}N_3S$: C, 73.20; H, 11.23; N, 8.83; Found: C, 73.29; H, 11.31 N, 8.90.

3-Decyl-7-undecylidene-4,5,6,7-tetrahydrobenzo[b]thiophene-2(3H)-thione **5**

A mixture of cyclohexanone derivative **1** (0.01 mole), and carbon disulfide (0.01mole) is added to methanol (50mL) containing potassium hydroxide (1.5 gm). The reaction mixture is refluxed for one hour. Then, the reaction mixture is evaporated under reduced pressure. The solid formed is extracted with ether. The ether extract is evaporated to give thiophene derivative **5**.

Yield: 60%; IR (KBr) cm^{-1}, ν: 1655 (C=C); ^{1}H NMR (DMSO) δ/ppm: 0.05 (m, 36H, $18CH_2$), 0.90 (m, 2H, CH_2), 1.20 (t, 6H, j=8 Hz, $2CH_3$), 2.10 (t, 4H, j=7.1 Hz, $2CH_2$), 2.30 (t, 1H, j=7 Hz, CH), 7.20 (t, 1H, j=6.1 Hz, CH=). ^{13}C NMR (DMSO) δ/ppm: 17.1, 17.8, 18.0, 19.1, 19.7, 20.1, 21.9, 22.0, 22.1, 23.1, 23.6, 24.5, 25.3, 47.6 (CH, $21CH_2$, $2CH_3$), 120.1, 122.1, 124.5, 139.1 (4C=), 178.4 (C=S). MS (m/z): 462.8 (M^+, 54%). Anal. Calcd. for $C_{29}H_{50}S_2$: C, 75.26; H, 10.89; N, 13.85; Found: C, 75.33; H, 10.96 N, 13.93.

Preparation of indazole derivatives 6a,b

A mixture of cyclohexanone derivative **1** (0.01 mole), and hydrazine hydrate or hydroxylamine (0.01 mole) is added to methanol (50 mL). The reaction mixture is refluxed for one hour. Then, the reaction mixture is evaporated under reduced pressure. The residue is extracted with ether. The ether extract is evaporated under reduced pressure to give indazole derivatives **6a,b**.

3-Decyl-7-undecylidene-2,3,4,5,6,7-hexahydro-1H-indazole **6a**

Yield: 70%; IR (KBr) cm^{-1}, ν: 3485 (NH), 3410 (NH); ^{1}H NMR (DMSO) δ/ppm: 0.05 (m, 36H, $18CH_2$), 0.90 (m, 2H, CH_2), 1.20 (t, 6H, j=8 Hz, $2CH_3$), 1.20 (brs, 2H, 2NH), 2.10 (t, 4H, j=6.2 Hz, $2CH_2$), 2.80 (t, 1H, j=6.2 Hz, CH), 7.20 (t, 1H, j=6.2 Hz, CH=). ^{13}C NMR (DMSO) δ/ppm: 18.0, 18.9, 19.1, 19.8, 20.2, 20.9, 21.1, 22.1, 23.6, 23.9, 25.3, 26.4, 27.6, 45.1 (CH, $21CH_2$, $2CH_3$), 119.3, 119.8, 120.1, 140.1 (4C=). MS (m/z): 416.7 (M^+, 58%). Anal. Calcd. for $C_{28}H_{52}N_2$: C, 80.70; H, 12.58; N, 6.72; Found: C, 80.78; H, 12.67 N, 6.80.

3-Decyl-7-undecylidene-1,3,4,5,6,7-hexahydrobenzo[c]isoxazole **6b**

Yield: 72%; IR (KBr) cm^{-1}, ν: 3405 (NH); ^{1}H NMR (DMSO) δ/ppm: 0.05 (m, 36H, $18CH_2$), 0.85 (t, 6H, j=8 Hz, $2CH_3$), 1.20 (t, 4H, j=7.1 Hz, $2CH_2$), 1.60 (m, 2H, CH_2), 3.80 (t, 1H, j=7 Hz, CH), 6.40 (brs, 1H, NH), 7.20 (t, 1H, j=6.2 Hz, CH=). ^{13}C NMR (DMSO) δ/ppm: 18.1, 18.9, 19.2, 19.9, 20.0, 20.8, 21.1, 21.9, 22.1, 22.8, 23.6, 23.9, 25.3, 47.6 (CH, $21CH_2$, $2CH_3$), 120.1, 122.0, 125.3, 137.9 (4C=). MS (m/z): 417.7 (M^+, 38%). Anal. Calcd. for $C_{28}H_{51}CNO$: C, 80.51; H, 12.31; N, 3.35; Found: C, 80.62; H, 12.40 N, 3.41.

2-((4-Chlorobenzylidene)hydrazono)-4-decyl-8-undecylidene-1,2,3,4,5,6,7,8-octahydroquinazoline **7**

A mixture of quinazoline derivative **3b**, and p-chlorobenzaldehyde (0.01 mole) is added to absolute ethanol (50 mL) containing acetic acid (5mL). The reaction mixture is refluxed for eight hours. The reaction mixture is evaporated under reduced pressure, and then extracted with ether. The ether extract is evaporated to give quinazoline derivative **7**.

Yield: 70%; IR (KBr) cm^{-1}, ν: 3470 (NH), 3430 (NH); ^{1}H NMR (DMSO) δ/ppm: 0.05 (m, 36H, $18CH_2$), 0.90 (t, 4H, j=7.1 Hz, $2CH_2$), 1.10 (t, 6H, j=8 Hz, $2CH_3$), 1.10 (brs, 2H, 2NH), 2.00 (m, 2H, CH_2), 3.90 (t, 1H, j=7 Hz, CHN), 5.00 (s, 1H, CH=), 7.48 (d, 2H, j=7.5 Hz, Ar), 7.75 (d, 2H, j=7.5 Hz, Ar), 8.10 (s, 1H, CH=N). ^{13}C NMR (DMSO) δ/ppm: 18.1, 18.4, 19.2, 19.5,

20.1, 20.9, 21.1, 22.1, 22.5, 23.6, 25.3, 26.0, 27.6, 46.3 (CH, 21CH_2, 2CH_3), 115.1, 120.1, 122.8, 126.1, 126.7, 130.3, 132.5, 141.9 (10 C=), 148.1, 169.0 (2C=N). MS (m/z): 581.3 (M^+, 61%). Anal. Calcd. for $C_{36}H_{57}ClN_4$: C, 74.38; H, 9.88; N, 9.64; Found: C, 74.45; H, 9.96 N, 9.71.

Preparation of quinazoline derivatives 8a,b

A mixture of quinazoline derivative **3b**, and ribose or glucose (0.01 mole) is added to absolute ethanol (50 mL) containing acetic acid (5mL). The reaction mixture is refluxed for eight hours. The reaction mixture is evaporated under reduced pressure, and then extracted with ether. The ether extract is evaporated to give quinazoline derivatives **8a,b**.

5-((4-Decyl-8-undecylidene-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-ylidene)hydrazono)pentane-1,2,3,4-tetraol **8a**

Yield: 70%; IR (KBr) cm^{-1}, ν: 3550 (OH), 3470 (NH), 3420 (NH); ^{1}H NMR (DMSO) δ/ppm: 0.80 (t, 6H, j=8 Hz, 2CH_3), 0.90 (m, 36H, 18CH_2), 1.20 (t, 4H, j=7.1 Hz, 2CH_2), 1.51 (m, 2H, CH_2), 2.80 (t, 1H, j=7 Hz, CHN), 3.40 (t, 2H, j=7 Hz, 2CHOH), 3.55 (m, 1H, CHOH), 3.70 (d, 2H, CH_2OH), 3.80 (brs, 4H, 4OH), 6.50 (t, 1H, j=6.2 Hz, CH=), 7.20 (d, 1H, CH=N), 8.20 (brs, 2H, 2NH). ^{13}C NMR (DMSO) δ/ppm: 18.1, 18.5, 19.0, 19.8, 20.3, 21.0, 22.1, 23.6, 24.1, 24.9, 25.3, 27.6, 30.8, 33.2 (CH, 21CH_2, 2CH_3), 61.2, 65.3, 69.3, 70.1 (4COH), 118.5, 119.8, 120.5, 131.9 (4C=), 158.1, 161.5 (2C=N). MS (m/z): 590.8 (M^+, 61%). Anal. Calcd. for $C_{34}H_{62}N_4O_4$: C, 69.11; H, 10.58; N, 9.48; Found: C, 69.20; H, 10.67 N, 9.56.

6-((4-Decyl-8-undecylidene-3,4,5,6,7,8-hexahydroquinazolin-2(1H)-ylidene)hydrazono)hexane-1,2,3,4,5-pentaol **8b**

Yield: 65%; IR (KBr) cm^{-1}, ν: 3580 (OH), 3460 (NH), 3427 (NH); ^{1}H NMR (DMSO) δ/ppm: 0.05 (m, 36H, 18CH_2), 0.90 (t, 6H, j=8 Hz, 2CH_3), 1.20 (m, 2H, CH_2), 1.50 (t, 4H, j=7.1 Hz, 2CH_2), 3.20 (t, 1H, j=7 Hz, CHN), 3.50 (t, 3H, j=7 Hz, 3CHOH), 3.65 (m, 1H, CHOH), 3.80 (d, 2H, CH_2OH), 4.10 (brs, 2H, 2NH), 6.36 (t, 1H, j=6.2 Hz CH=), 7.30 (d, 1H, j=6.2 Hz, CH=N), 8.20 (brs, 5H, 5OH). ^{13}C NMR (DMSO) δ/ppm: 17.0, 17.6, 18.4, 19.3, 20.5, 22.1, 23.6, 23.9, 24.0, 25.3, 27.6, 29.5, 30.6, 34.2 (CH, 21CH_2, 2CH_3), 61.2, 65.3, 69.3, 70.1, 73.6 (5 COH), 119.1, 120.1, 122.5, 139.9 (4C=), 158.1, 163.0 (2C=N). MS (m/z): 620.9 (M^+, 49%). Anal. Calcd. for $C_{35}H_{64}N_4O_5$: C, 67.70; H, 10.39; N, 9.02; Found: C, 67.81; H, 10.47 N, 9.10.

Biological activity (antimicrobial activity)

The antimicrobial activity of various compounds **1-7** were tested using agar well diffusion method on Muller Hinton agar medium (MHA, India) for bacteria. For C. albicans and F. oxysporum, we used agar diffusion method on potato dextrose agar medium. 100 µL of 24 h. culture of gram negative and gram positive bacteria were distributed with sterilized glass rod on surface of MHA plates. Then, agar wells (8mm diameter) were cut in the inoculated lates and 100 µ of each compound were loaded in the wells individually using a sterile cork borer. Dimethylsulfoxide (DMSO) was used as a control solvent. The plates were stand for two hours at 4 ºC followed by incubation at 37 ºC for 18-24 h.. Then, inhibition zones were measured (13). The bacteria used were obtained from bacteriology lab. at botany and microbiology department, faculty of science, Al-Azhar University. The fungi used were obtained from mycology lab. at botany and microbiology department, faculty of science, Al-Azhar University.

3. Results and Discussion

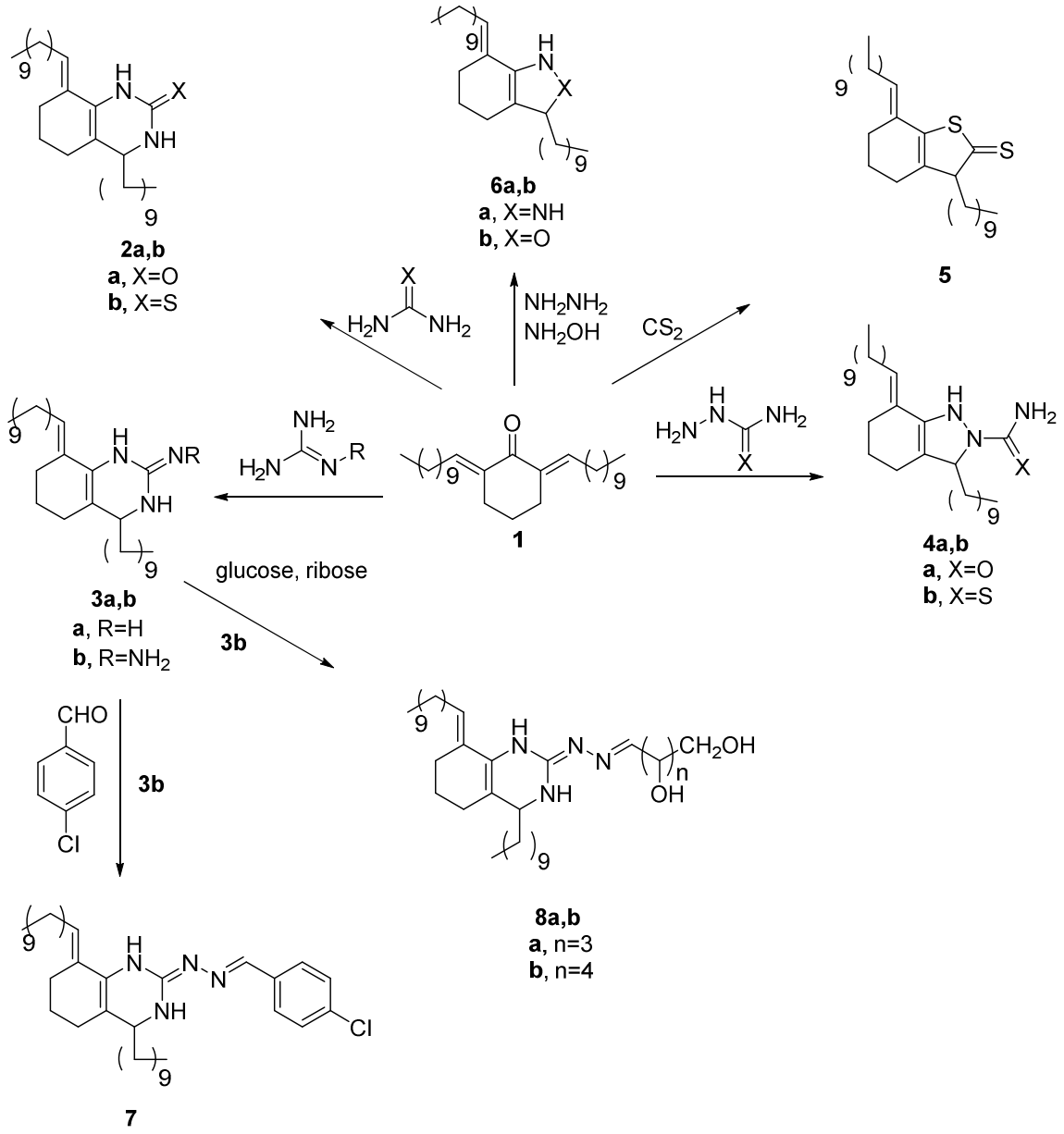
A- Chemistry

Cyclohexanone reacts with undecanal to afford 2,6-diundecylidenecyclohexan-1-one **1**. 2,6-Diundecylidenecyclohexan-1-one **1** reacts with urea, and thiourea to afford quinazoline derivatives **2a,b**. Cyclohexanone derivative **1** reacts with guanidine, and aminoguanidine to form quinazoline derivatives **3a,b**. Spectroscopic data (MS, IR, ^{1}H & ^{13}C NMR) are in agreement with the structures proposed. Compound **1** shows chemical shift corresponding to C=CH at δ 5.00 ppm in the ^{1}H NMR. Also, compound **1** shows chemical shift corresponding to C=C at δ 148.1, 151.1 ppm in the ^{13}C NMR. Quinazoline derivatives **2a** shows absorption band corresponding to carbonyl group, and amino groups in the infrared spectrum. Compound **2** shows characteristic chemical shift at δ 4.80 ppm corresponding to CHN in the ^{1}H NMR. Quinazoline derivative **2a** shows characteristic chemical shift at δ 151.4 ppm corresponding to carbonyl group in ^{13}C NMR. The IR spectra of quinazoline derivative **3a** shows absorption band corresponding to amino groups. The ^{1}H NMR of compound **3a** shows chemical shift at δ 3.60 ppm corresponding to CHN. The ^{13}C NMR of compound **3a** show chemical shift at δ 156.4 ppm corresponding to C=N.

Compound **1** reacts with semicarbazide, and thiosemicarbazide to give indazole derivatives **4a,b**. Also, cyclohexanone derivative **1** reacts with carbon disulfide to afford benzo[b]thiophene derivative **5**. Cyclohexanone derivative **1** reacts with hydrazine hydrate, and hydroxylamine to form indazole derivatives **6a,b**. The structures of indazole derivatives **4a,b, 6a,b**, and benzo[b]thiophene derivative **5** were confirmed from MS, IR, and ^{1}H & ^{13}C NMR spectral data. The infrared spectrum of indazole derivative **4a** shows absorption band for amino groups and amide group. The ^{1}H NMR of indazole derivative **4a** shows chemical shift at δ 3.60 ppm corresponding to CHN. The ^{13}C NMR of indazole derivative **4a** shows chemical shift at δ 161.1 ppm corresponding to carbonyl group. The infrared spectrum of benzo[b]thiophene derivative **5** shows disappearance of absorption band of carbonyl function group. The ^{13}C NMR of compound **5** show chemical shift at δ 178.4 ppm corresponding to C=S group. The infrared spectrum of indazole derivative **6a** shows disappearance of absorption band of carbonyl group and appearance of absorption band for amino groups. The ^{1}H NMR of compound **6a** shows chemical shift at δ 2.80 ppm corresponding to CHN.

Quinazoline derivative **3b** reacts with p-chlorobenzaldehyde to afford octahydroquinazoline derivative **7** (**Scheme 1**). Also, quinazoline derivative **3b** reacts with ribose, and glucose to afford sugar derivatives **8a,b**. Spectroscopic data of quinazoline derivatives **7**, and **8a,b** are in agreement with the structures proposed. In compound **7**, the absorpance of

aminogroup (-NH_2) has been disappeared. Quinazoline derivative **7** shows characteristic signal corresponding to CH=N at δ 8.10 ppm. The infrared spectra of quinazoline derivatives **8a,b** show absorption bands corresponding to hydroxyl groups. The ^{1}H NMR of quinazoline derivative **8a** shows characteristic signal at δ 7.20 ppm corresponding to CH=N.



Scheme 1

B- Biological activity (antimicrobial activity)

The antimicrobial activity of compounds **1-7** against bacterial and fungal microorganisms were screened using the agar well diffusion assay (Table 1) (14).The antimicrobial activities of the compounds are listed in Table 1. Most compounds have good activity against tested bacterial and fungal microorganisms. Quinazoline derivative **8b** has activity against S. aureus more than standard drug. Compounds **2a, 4a**, and **8a,b** have activity against B. cereus more than standard drug used. Compounds **1, 2a,b, 3a,b, 4a,b, 5**, and **8a,b** show activity towards K. pneumonia more than standard drug used. Compound **6b** show activity towards C. albicans more than standard drug used. Compounds **1, 4a,b, 5, 6a,7**, and **8a** show activity towards F. oysporum more than standard drug used. Sugar moiety derived from glucose in quinazoline derivative **8b** results in promising activity

against S.aureus. Carbonyl group in quinazoline derivative **2a**, and indazole derivative **4a** results in promising activity against B. cereus. Sugar moiety in quinazoline derivatives **8a,b** produce potent activity towards B. cereus more than standard drug used. α,β-Unsaturated carbonyl group in compound **1** results in promising activity against K. pneumonia. Urea and thiourea moiety in quinazoline derivative **2a,b** produce good activity towards K. pneumonia. Also, guanidine and aminoguanidine moiety in compound **3a,b** produce promising effect towards K. pneumonia. Thiosemicarbazide and semicarbazide in indazole derivative **4a,b** results in promising activity towards K. pneumonia. Carbon atom linked to two sulfur atoms give promising activity of benzo[b]thiophene derivative **5** towards K. pneumonia.

Table 1: The antimicrobial activity of various compounds

Different compounds	Inhibition zone Diameter mm ± SE					
	Gram Positive Bacteria		*Gram Negative Bacteria*		*Fungi*	
	S aureus	***B cereus***	***E coli***	***K pneumonia***	**C albicans**	***F oxysporum***
1	27.5 ±0.2	16.1±0.7	19.6±0.3	18.8±0.4	20±0.5	15.1±0.4
2a	25±2.5	20±0.5	17.5±0.2	18±0.5	20±1.1	18±0.5
2b	27.3±0.3	16±0.2	21.1±0.7	17±0.8	20±0.5	17.1±0.7
3a	25.3±0.3	17.1±0.7	21±0.5	19±0.5	20±0.5	18.1± 0.4
3b	25.5±0.2	20±0.5	22.1±0.6	21.1±0.7	21.3±0.8	17.1±0.4
4a	23±0.2	16±0.5	17.1±0.7	18.1±0.7	18±0.5	13±0.5
4b	26±1.15	15±0.2	20.8±0.6	17±0.5	21.3±0.8	12±0.5
5	26±0.8	18±0.8	22.5±1.0	18.1±0.7	22.3±0.8	12.3±0.6
6a	26±0.5	17.1±0.7	20±0.5	19.1±0.4	20±0.5	14.3±0.4
6b	23.1±0.7	18±0.5	22.1±0.4	22.3±0.4	13±0.5	0
7	23.1±0.4	20.5±0.5	22±0.5	30.1±1.0	18.3±0.6	11.5±0.2
8a	19.1±0.6	17.6±0.4	18.1±0.4	30.3±1.0	17.1±0.6	11.6±0.3
8b	17.1±0.4	15±0.5	17±0.5	21.1±0.7	17.5±0.5	17±0.2
Ciprofloacin	18.1± 0.7	13±0.5	19.1±0.4	22 ±0.5	15.3±0.8	16.1±0.6
Control (DMSO)	0	0	0	0	0	0

Conflict of interest

The authors declare no conflict of interest.

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